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overgrowth (SIBO) by administering an agent that modifies afferent neural feedback or sensory perception.

REMARKS

The Pending Claims:

Before entry of the preceding amendments, Claims 12-30 and 56-66 are pending in this application. Claims 12-30 and 56-66 are directed to a method of treating irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, an autoimmune disease, or Crohn's disease.

The Office Action and Applicant's Response

The Examiner acknowledged Applicant's election of designated claim Group II (Claims 12-30 and 56-66), and the election of species, under 35 U.S.C. § 121, which species include a prokinetic agent, a macrolide (or so-called "motilide") compound, erythromycin, an agent that modifies afferent neural feedback or sensory perception, a 5-HT receptor antagonist, and alosetron.

The Examiner noted the claims within Group II would only be examined to the extent of the elected species, however, the Examiner had previously stated that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species. Applicant reiterates, in concurrence with the Examiner's earlier statement in the Office Action mailed March 22, 2001, that in elected Group II, allowable generic claims exist in the application, for example, Claim 12 (e.g., at pages 3-4 of Office Action mailed 3/22/01).

The Examiner noted that the application was filed with informal drawings, and she stated that formal drawings will be required when the application is allowed. Applicant brings the Examiner's attention to the three sheets of formal drawings

(Figures 1-6) that Applicant mailed on January 23, 2001.

The Examiner stated that no claims were allowed, and she cited the following grounds of rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 12-30 and 56-58 were rejected, 35 U.S.C. § 112, second paragraph. The Examiner stated that the claims were vague and indefinite in the recitation of "SIBO" and that a skilled artisan would be unable to determine the metes and bounds of such a limitation. Without a clear definition of SIBO, the Examiner stated that the skilled artisan would be unable to replicate the claims.

Claim 12 recites the step of detecting the presence of "*small intestinal bacterial overgrowth.*" Claim 56 recites the limitation in an alternative form, "SIBO". Applicant disagrees that the expressions "small intestinal bacterial overgrowth" or "SIBO" are indefinite. For example, the specification as originally filed provides a clear definition of small intestinal bacterial overgrowth (SIBO), e.g., at page 15, lines 20-28, where it states "[n]o association has ever been made between any of the afore-going diagnostic categories and small intestinal bacterial overgrowth (SIBO). SIBO, also known as small bowel bacterial overgrowth (SBBO), is an abnormal condition in which aerobic and anaerobic enteric bacteria from the colon proliferate in the small intestine, which is normally relatively free of bacterial contamination." Notably, the specification also cites an art-recognized definition that "SIBO is defined as greater than 10^6 CFU/mL small intestinal effluent (R.M. Donaldson, Jr., *Normal bacterial populations of the intestine and their relation to intestinal function*, N. Engl. J. Med. 270:938-45 [1964])." (at page 15, lines 24-26). The specification states that "[t]ypically, the symptoms include abdominal pain, bloating, gas and alteration in bowel habits, such as constipation and diarrhea." (at page 15, lines 26-28). The specification, as originally

filed, also provides detailed descriptions of methods for detecting small intestinal bacterial overgrowth (SIBO), for example, at page 21, line 3 through page 23, line 14. Thus, the limitations recited in Claim 12, "small intestinal bacterial overgrowth" or Claim 56, "SIBO", are clear to the skilled artisan who would indeed be able to replicate the claims, especially in view of the detailed description of Applicant's specification.

Nevertheless, merely by way of refinement to Claims 56 and 57, and for the sake of greater clarity, Applicant has amended Claims 56 and 57 to recite "small intestinal bacterial overgrowth (SIBO)", instead of merely reciting the acronym "SIBO". The Examiner is respectfully requested to withdraw the rejection based on this ground.

The Examiner also asserted that the claims are vague and indefinite for the recitation of "whereby the symptom(s) is improved" (e.g., last line of Claim 12). She stated that without a clear definition of what constitutes an improvement, a skilled artisan would be unable to replicate the claims. Applicant strongly disagrees that the limitation "improved" is unclear, based on Applicant's disclosures in the specification as originally filed. For example, the specification, at page 20, line 6 through page 21, line 2, describes suitable diagnostic criteria for irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, depression, ADHD, SLE, multiple sclerosis, and Crohn's disease are cited. Notably, e.g., at page 20, lines 8-10, the specification directs the skilled artisan to the art-recognized Rome criteria for irritable bowel syndrome (IBS) (Thompson *et al.*, *Irritable bowel syndrome: pathogenesis and management*, Lancet 341:1569-72 [1993]).

Further, the specification states that "[a]fter the SIBO condition is at least partially eradicated, typically within a couple of weeks, there is an improvement in the symptom(s) . . ." of these disorders (at page 23, lines 19-22). The specification goes on to say that "[i]t is a benefit of the present treatment method that after treatment, subjects routinely report feeling better that they have felt in years" (at page 23, lines 22-24),

which is demonstrated in numerous patients in Examples 1-10 and by Figures 1-6, with respect to appropriately representative symptoms. Moreover, at page 29, at about lines 12-26, the specification particularly states:

> . . . Improvement in a symptom(s) is typically determined by self-reporting by the human subject, for example by VAS scoring or other questionnaire. Improvement in academic, professional, or social functioning, e.g., in cases of ADHD or depression can also be reported by others or can be observed by the clinician. Improvement (increase) in pain threshold, e.g., in subjects diagnosed with fibromyalgia, can be measured digitally, for example, by tender point count, or mechanically, for example, by dolorimetry. (F. Wolfe *et al.*, *Aspects of Fibromyalgia in the General Population: Sex, Pain Threshold, and Fibromyalgia Symptoms*, J. Rheumatol. 22:151-56 [1995]). Improvement in visceral hypersensitivity or hyperalgesia can be measured by balloon distension of the gut, for example, by using an electronic barostat. (B.D. Nabiloff *et al.*, *Evidence for two distinct perceptual alterations in irritable bowel syndrome*, Gut 41:505-12 [1997]). Some improvement(s) in symptoms, for example systemic lupus erythematosus symptoms, such as rashes, photosensitivity, oral ulcers, arthritis, serositis, or improvements in the condition of blood, kidney or nervous system, can be determined by clinical observation and measurement.

With respect to the symptoms of the recited disorders which are known to the skilled artisan, as shown above, Applicant is entitled under the patent law to rely on the commonly understood meaning of "improved", such as "relieved", "alleviated", "palliated", "assuaged", "made better", "ameliorated", "helped", "aided", "upgraded", "healed" and "mended", among many common dictionary examples pertaining to improvement in a patient's symptoms. Applicant provides some examples of common synonyms for the word "improved," which Applicant took from the Internet, but these are by no means exhaustive. **(Exhibit A)**.

Therefore, Applicant asserts that the skilled artisan is indeed capable of knowing what constitutes an "improvement" in the symptoms of the human subject. The Examiner is respectfully requested to withdraw the rejection on this ground.

Claims 12 and 27 were rejected for the recitation of the phrase "substantially simultaneously." Contrary to the Examiner's assertion, Claim 12 entirely lacks the offending phrase. For the sake of clarity, Applicant has amended Claims 27 and 29 to delete the word "substantially." Therefore, the Examiner is respectfully requested to withdraw the rejection on this ground.

Rejections under 35 U.S.C. § 102(b)

Claims 12-30 and 56-58 were rejected for a purported lack of novelty over three patents: (1) McCann *et al.* (U.S. Patent No. 5,599,795); (2) Sandborn (U.S. Patent No. 5,691,343); and (3) Becker *et al.* (U.S. Patent No. 5,612,366).

A claim is anticipated only if each and every element as set forth in the claim is found in a single prior art reference. *Verdgaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

(1) Rejection over McCann *et al.* (U.S. Patent No. 5,599,795)

The Examiner asserted that the McCann *et al.* patent "discloses a method of treating irritable bowel syndrome comprising detecting the presence of intestine [sic] bacterial overgrowth in a human subject with Crohn's disease. McCann *et al.* further disclose a method of treating *Bifidobacterium* with antibiotics."

Applicant strongly disagrees that the McCann *et al.* patent negates novelty. Contrary to the Examiner's assertion, McCann *et al.* patent is directed to a method of treating *idiopathic inflammatory bowel disease* (IIBD)(e.g., column 1, lines 63-66; Claim 1 of McCann *et al.*), but not to *irritable bowel syndrome* (IBS).

Also, Applicant's claimed method includes the step of "detecting the presence of

small intestinal bacterial overgrowth in a human subject having at least one symptom associated with a suspected diagnosis of irritable bowel syndrome, etc. . ." (e.g., Claim 12 and claims directly or indirectly dependent therefrom). The cited McCann *et al.* patent fails to include a step of detecting the presence of small intestinal bacterial overgrowth. Thus, McCann *et al.* fails to anticipate each and every element as set forth in Applicant's Claim 12.

Consequently, McCann *et al.* fails to anticipate Applicant's claimed method.

Therefore, the Examiner is respectfully requested to withdraw the rejection on this ground.

(2) Rejection over Sandborn (U.S. Patent No. 5,691,343)

The Examiner asserted that the cited Sandborn patent discloses a method of treating irritable bowel syndrome, which method involves the administration of a 5-aminosalicylate compound.

Again, Applicant strongly disagree that Sandborn anticipates the claimed method. Contrary to the Examiner's assertion, the cited Sandborn patent describes a method of treating *inflammatory bowel disease* (IBD)(e.g., column 1, lines 34-38), not irritable bowel syndrome (IBS). The method of Sandborn involves topically administering to the colon . . . enterically coated azathioprine (e.g., Claim 1 of Sandborn). In a single passage, upon which the Examiner has focused, the Sandborn patent does discuss reduced colonic absorption of *5-aminosalicylate* compared to azathioprine and 6-mercaptopurine (e.g., column 6, line 67 through column 8, line 8), but Sandborn fails to describe the use of 5-aminosalicylate in the treatment of irritable bowel syndrome or small intestinal bacterial overgrowth (SIBO).

Importantly, Applicant's claimed method includes the step of "detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one

symptom associated with a suspected diagnosis of irritable bowel syndrome, etc. . ." (e.g., Claim 12 and claims directly or indirectly dependent therefrom). The cited Sandborn patent fails to include a step of detecting the presence of small intestinal bacterial overgrowth. Thus, Sandborn fails to anticipate each and every element as set forth in Applicant's Claim 12.

Consequently, Sandborn fails to anticipate Applicant's claimed method.

Therefore, the Examiner is respectfully requested to withdraw the rejection on this ground.

(3) Rejection over Becker *et al.* (U.S. Patent No. 5,612,366)

Presumably with respect to Claims 56-58, the Examiner stated that the Becker *et al.* patent "discloses a method of treating irritable bowel syndrome by administering a prokinetic agent wherein the agent is a 5-HT receptor antagonist."

Applicant strongly disagrees that the cited Becker *et al.* patent negates the novelty of Applicant's claimed method. Applicant's claimed method includes the step of "detecting the presence of small intestinal bacterial overgrowth in a human subject having at least one symptom associated with a suspected diagnosis of irritable bowel syndrome, etc. . ." (e.g., Claim 12 and claims directly or indirectly dependent therefrom). The cited Becker *et al.* patent fails to include a step of detecting the presence of small intestinal bacterial overgrowth. Thus, Becker *et al.* fails to anticipate each and every element as set forth in Applicant's Claim 12.

Consequently, Becker *et al.* fails to anticipate Applicant's claimed method.

Therefore, the Examiner is respectfully requested to withdraw the rejection on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this

application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend Claims 27, 29, 56, and 57 as follows.

27.(Amended) The method of Claim 12, wherein the suspected diagnosis is of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, attention deficit/hyperactivity disorder, or an autoimmune disease; and further comprising administering to said human subject an antagonist of a pro-inflammatory cytokine or an antibody that specifically binds an inflammatory cytokine, [substantially] simultaneously with or after at least partially eradicating small intestinal bacterial overgrowth in the human subject.

29.(Amended) The method of Claim 12, further comprising administering to said human subject an anti-inflammatory cytokine or an agonist thereof, [substantially] simultaneously with or after at least partially eradicating small intestinal bacterial overgrowth in the human subject.

56.(Amended) The method of Claim 12, wherein the symptom is hyperalgesia related to small intestinal bacterial overgrowth (SIBO).

57.(Amended) The method of Claim 56, further comprising alleviating or improving the hyperalgesia related to small intestinal bacterial overgrowth (SIBO) by administering an agent that modifies afferent neural feedback or sensory perception.